Opioid Cohort Consortium (OPICO) to investigate the effects of regular opioid use on mortality and on cancer development

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Outline

● Overview of the project and its aims
● Engaging LMIC cohorts
● Challenges and solutions
● What went well (wins)
● Plans for publications
● Call for participation
Global crisis of opioid use

- Thousands of deaths and billions in economic losses each year
- Long-term health consequences remain unknown
Opioids Definition

- **Natural opioids ( opiates):** opium and its natural derivatives
- **Semi-synthetic opioids:** synthesized in labs from natural opioids
- **Synthetic opioids:** synthesized in labs using the same chemical structures of natural opioids to mimic their effects

<table>
<thead>
<tr>
<th>Natural prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine, Codeine, Thebaine, Powdered Opium, Opium syrup</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semi-synthetic prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzhydrocodone, Desomorphine, Diamorphine, Dihydromorphine, Dihydrocodeine, Etorphine, Ethylmorphine, Hydrocodone, Hydromorphone, Nalbuphine, Nalorphine, Nicomorphine, Oxycodone, Oxymorphone,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synthetic prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil, Alphaprodine, Alphacetylmethadol, Bezitramide, Buprenorphine, Butorphanol, Carfentanil, Dezocine, Dextromoramide, Dextropropoxyphene, Dihydroetorphine, Diphenoxylate, Dipipanone, DPDPE, Eluxadoline, Fentanyl, Ketobemidone, Levacetylmethadol, Levorphanol, Lofentanil, Meptazinol, Methadone, Methadyl acetate, Normethadone, Noscapine, Oliceridine, Papaveretum, Pentazocine, Pethidine (Meperidine), Piritramide, Phenazocine, Phenoperidine, Remifentanil, Sufentanil, Tapentadol, Thebaine, Tilidine, Tramadol</td>
</tr>
</tbody>
</table>
Scientific motivation

Opioids used by 58 million (2018)

**Opiates (mainly Opium)** used by 30 million (2018)

- Human studies
  - 2 Cohort
  - 30 Case control
  - Association with at least 9 cancer types
  - Genotoxicity
    - Carcinogenic compounds

- Experimental studies

**Prescription opioids**

- Human studies
  - 6 Registry data linkage
  - Association with several cancer types (lung, urogenital, liver)
  - Genotoxicity
  - Tumor promotion
    - Involvement in tumor initiation and progression

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Opium consumption classified by IARC Monographs into Group1 / Carcinogen to humans

Many limitations in the current evidence on opioid effects
- Confounding effects and biases from linkage studies
- No opioid use data in most cohorts
- Limited number of opioid users in cohorts with opioid use data

Comprehensive consortium-based approach is needed
Overview of the Opioid Cohort Consortium (OPICO)

Grant support

- International Hundred K+ Cohort Consortium / Global Genomic Medicine Collaborative

Overarching aim

- To build a strong international resource for multidisciplinary scientific studies on the use of opioids and their long-term effects

Main exposure

- Use of prescription opioids from medication questionnaire
- Use of prescription opioids from linkage to national medication dispensing records

Main outcomes

- **Cancer analysis**: diagnosis of any cancer type / digestive cancers / respiratory cancers / urinary tract cancers / brain cancer
- **Mortality analysis**: death from any cause / death from circulatory diseases / respiratory diseases / digestive diseases / cancer

Aims & Approach

- Organize data on opioid use from prospective cohorts
- Compile data on opioid use in cohorts through linkage to national records
- Assess the type, distribution, and extent of opioid use across diverse populations
- Determine the association of opioid use with cancer incidence and mortality
OPICO cohorts (n=1,266,247 participants)

- UK Biobank (n = 502,713)
- PLCO (n = 58,895)
- Constances cohort (n = 217,000)
- Generation Scotland (n = 24,000)
- Golestan (n = 50,045)
- Pars (n = 9,264)
- WHI (n = 93,676)
- EPIC (n = 100,000)
- PERSIAN (n = 172,894)
- 45 & UP (n = 37,760)
### Cohorts with medication data participating in OPICO

<table>
<thead>
<tr>
<th>Cohort Study</th>
<th>Participants (N)</th>
<th>Total opioid users N (%)</th>
<th>Medication data</th>
<th>Linkage source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golestan cohort</td>
<td>50,045</td>
<td>8,519 (17.0%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>PERSIAN cohort</td>
<td>172,894</td>
<td>21,557 (12.4%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>45 and up cohort</td>
<td>37,760</td>
<td>8,603 (22.7%)</td>
<td>Linkage</td>
<td>PBS (Australia)</td>
</tr>
<tr>
<td>UK Biobank cohort</td>
<td>502,713</td>
<td>25,864 (5.1%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>Scottish Family Health Study</td>
<td>24,000</td>
<td>2,082 (8.6%)</td>
<td>Linkage</td>
<td>SPI (Scotland)</td>
</tr>
<tr>
<td>Pars cohort</td>
<td>9,264</td>
<td>818 (8.8%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>PLCO Cancer Screening Trial</td>
<td>58,895</td>
<td>25,187 (42.7%)</td>
<td>Linkage</td>
<td>Medicare (USA)</td>
</tr>
<tr>
<td>Women Health Initiative (WHI)</td>
<td>93,676</td>
<td>8,430 (8.9%, estimated)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>EPIC (French)</td>
<td>100,000</td>
<td>4,000 (4%, estimated)</td>
<td>Linkage</td>
<td>Insurance Plan</td>
</tr>
<tr>
<td>CONSTANCES</td>
<td>217,000</td>
<td>8,680 (4%, estimated)</td>
<td>Linkage</td>
<td>CNDS (France)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,266,247</strong></td>
<td><strong>113,740 (8.9%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Challenges and solutions (1)

**Challenge:**
Defining opioid exposure and coding opioids medications
- Different names (brad & generic names)
- Different countries
- Different data sources (questionnaires & national records)
- Different coding systems

**Solution:**
- Working closely with local expert pharmacoepidemiologists in each country
- Using the WHO classification system (The Anatomical Therapeutic Chemical (ATC) Classification System)
- Using available online mapping resources (online WHO tool, user-defined R packages, available publications and codes from previous researches)
Challenges and solutions (2)

Challenge:
Harmonizing opioid exposure data
• Different sources: questionnaire data (lifelong medication use data) vs. Registry based data (data over a limited period)
• Different types: different type and routes of opioids

Solution:
• Defining a timeline of 12 months before recruitment as the time of exposure to opioids
• Assessing the effects of long-term use vs. short-term use
• Assessing the effects of using strong vs. weak opioids
• Harmonizing different opioids based on the Oral Morphine Equivalent unit (OME)
• Assessing the cumulative used opioids
Challenges and solutions (3)

Challenge:
• Some included cohorts cannot send their linked data to IARC due to their national regulations for data protection and security

Solution:
• Using an additional distributed analysis model
• Analyze the data from these cohorts using the corresponding secure platform
• Perform meta-analyses using the aggregated outputs from these cohorts
Wins: feasibility of compiling opioid use data in cohorts with linkage

Collaboration with:
- Cancer Council NSW, Australia (Prof. Canfell, Dr. Weber, Dr. Sarich)
- University of NSW Sydney (Prof. Pearson)

Australian 45 and Up Study
- Recruited 267,153 adults (2006 – 2009) / General population of NSW

Linked to the Pharmaceutical Benefits Scheme (PBS)
- Australia’s national drug subsidy program
Lessons learned from the feasibility study:

Identification of the:

- policy of medication dispensing / subsidy program
- pricing of opioids at the time of cohort recruitment

Reasons:

- To minimize the possible misclassifications
- To identify the inclusion and exclusion criteria

Example from the Feasibility Study:

Australia → co-payment program for prescriptions
- different thresholds for ‘concessional beneficiaries’ vs. ‘general beneficiaries’

In 2008 (45 and up recruitment period):

- Co-payment for ‘concessional beneficiaries’ = $5.00
- Co-payment for ‘general beneficiaries’ = $31.30.
- Many opioid medications in Australia are priced $20 - $25
- These medications were not recorded in the linked national data source (PBS database) when dispensed to general beneficiaries.

- Only 37,760 participants who were concessional beneficiaries at recruitment were included

- We compiled opioid use for all included participants, of whom 8,603 (22.8%) were users of opioids
Plans for publications

- Consortium Profile

- Methodology paper on the methods of compiling opioid use data in prospective cohorts using linkage to national medication dispensing records
Required data from cohorts to participate in OPICO

- **Use of opioids**
  - questionnaires
  - data linkage to national records

- **Outcomes at follow-up**
  - vital status
  - cause of death
  - diagnosis of cancer
  - type of cancer

- **Dates or equivalent follow-up times**

- **Demographics**
  - age
  - sex
  - ethnicity
  - socioeconomic indicator

- **Smoking cigarettes**

- **Alcohol intake**

- **Chronic health conditions**
  - Diabetes
  - Hypertension
  - inflammatory conditions

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**IARC / Genomic Epidemiology Branch**

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